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A Novel Mannich-type Reaction: Lanthanide Triflate-Catalyzed Reactions of *N*-(α-Aminoalkyl)benzotriazoles with Silyl Enolates

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Abstract: *In the presence of a catalytic amount of a lanthanide triflate, N-(α-aminoalkyl)benzotriazoles reacted with silyl enolates to give the corresponding β-amino ketone or ester derivatives in high yields with high diastereoselectivities.*

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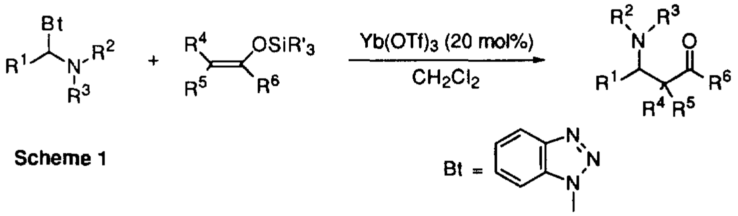
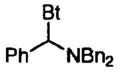
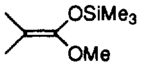
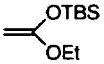
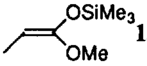
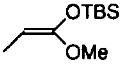
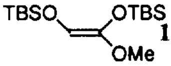
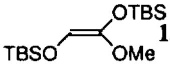
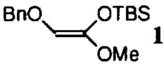
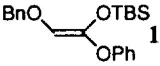
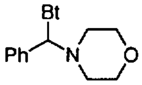
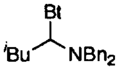
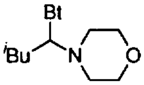
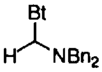
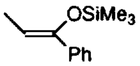
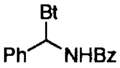
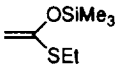
The Mannich and related reactions are among the most fundamental and useful of carbon-carbon bond forming reactions.[1] In the classical Mannich routes to β-amino ketones and esters, yields are sometimes low because significant side reactions, such as deamination, occur under the rather drastic reaction conditions. To perform the reactions under milder conditions, new modifications using preformed iminium salts[2] and imines[3] were introduced: however, these intermediates are often hygroscopic and/or thermally unstable, thus the development of a new method is still highly appropriate.

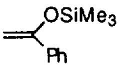
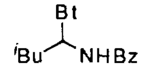
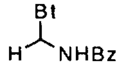
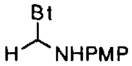
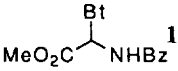
Recently, our group at Florida reported that *N*-(α-aminoalkyl)benzotriazoles behave as masked imines,[4] and that they react with lithium enolates to afford β-amino ketones[5] and esters.[6] While many kinds of β-amino ketones and esters were prepared according to these reactions, deamination and low yields were sometimes observed. Concurrently, our group at SUT discovered that lanthanide triflates, as Lewis acids stable in aqueous media[7] efficiently catalyze reactions of imines and other *N*-containing compounds.[8] While stoichiometric amounts of Lewis acids are frequently required for the activation of imines and *N*-containing compounds, a catalytic amount of a lanthanide triflate is sufficient to complete many such reactions. We have now found that lanthanide triflates are also effective for the activation of *N*-(α-aminoalkyl)benzotriazoles, and we now report a novel Mannich-type reaction of *N*-(α-aminoalkyl)benzotriazoles with silyl enolates using a lanthanide triflate as a catalyst.[9]



Scheme 1

Table 1. Reactions of *N*-(Aminoalkyl)benzotriazoles with Silyl Enolates

Entry	*N*-(Aminoalkyl)-benzotriazole	Silyl Enolate	Temp./°C	Yield/%	(*syn*/*anti*)^a
1	 **1**	 **11**	rt	85^b	
2	**1**	 **12**	rt	99	
3	**1**	 **13Z**	-78	99	(2/98)
4	**1**	 **14Z**	-78	72	(<2/>98)
5	**1**	 **15Z**	-78	99	(10/90)
6	**1**	 **15E**	rt	quant.	(17/83)
			0	98	(14/86)
			-78	94	(3/97)
7	**1**	 **16Z**	-78	97	(14/86)
8	**1**	 **17Z**	-78	quant.	(5/95)
9	 **2**	**11**	rt	97	
10	**2**	**15E**	-78	89	(<2/>98)
11	 **3**	**11**	rt	94	
12	**3**	**17Z**	-78	91	(30/70)
13	 **4**	**11**	rt	93	
14	 **4**	**11**	rt	91	
15	**4**	**12**	rt	87	
16	**4**	 **18**	rt	75	
17	 **6**	**11**	rt	98	
18	**6**	 **19**	rt	99	

19	**6**	 **20**	rt	60
20	 **7**	**11**	40	81
21	 **8**	**11**	80	75[c]
22	 **9**	**11**	rt	77
23	 **10**	**11**	rt	82[d]

[a] Determined by ^{1}H NMR. [b] 96% yield when $Sc(OTf)_3$ was used. [c] 1,2-Dichloroethane was used as a solvent. [d] Acetonitrile was used as a solvent.

The general scheme of these novel Mannich-type reactions of *N*-(α-aminoalkyl)benzotriazoles with silyl enolates is shown in Scheme 1. Selected examples are presented in Table 1, and the following characteristic features are noted:

(1) In all cases, the expected β-amino esters and ketones were obtained in high yields. Silyl enolates derived not only from esters, but also from thioesters and from ketones reacted smoothly with *N*-(α-aminoalkyl)benzotriazoles to give the adducts.

(2) Various reaction temperatures could be used in the range of -78 °C to 80 °C. No detectable side reactions occured even at elevated temperatures.

(3) No deamination occurred in these reactions. In the conventional Mannich reaction, deamination of Mannich bases to afford α,β-unsaturated derivatives is an undesirable side reactions, especially at higher temperatures.

(4) A variety of *N*-(α-aminoalkyl)benzotriazoles could be utilized in this reaction. Some of the adducts of the present reactions cannot be prepared by conventional imino aldol reactions of imines with enolate components.[3] Benzotriazole compounds derived from aromatic aldehydes reacted smoothly, as did aliphatic aldehydes (possessing enolizable protons). In addition, benzotriazole derivatives from formaldehyde and from methyl glyoxylate (whose imines are difficult to prepare[10]) reacted with silyl enolates to afford the corresponding adducts in high yields. The reaction of benzotriazole **9** with silyl enolate **11** (entry 21 of Table 1) was well controlled without side reaction adducts (especially, no further reaction of the product with **11**).

(5) Lanthanide triflates were the best catalysts, and all lanthanide triflates [$Ln(OTf)_3$; Ln = Sc, Y, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu] were effective in this reaction, providing >90% yield in the reaction of **2** with **11**. The triflates can be recovered and used repeatedly (1st run, 93% yield; 2nd run, 91% yield; 3rd run, 91% yield in the reaction of **4** with **11**).

(6) High *anti* diastereoselectivities were observed in the reactions of **1**, **2**, and **3** with silyl enolates **13**-**17**. Significantly, these high *anti*-selectivities were observed regardless of the geometry of the silyl enolates. However, **6** reacted with **15Z** and **15E** to afford the corresponding adducts in 97% and 86% yields, respectively, with lower selectivities (*syn*/*anti* = 66/34 and 56/44, respectively).

A typical experimental procedure is described for the reaction of **1** with **15E**; to Yb(OTf)$_3$ (0.05 mmol, 20 mol%) and **1** (0.25 mmol) in dichloromethane (1.5 ml) was added **15E** (0.38 mmol) in dichloromethane (0.5 ml) at -78 °C. The mixture was stirred at this temperature for 24 h, and water was then added. The organic layer was separated and the aqueous layer extracted with dichloromethane. After usual work up, methyl 3-dibenzylamino-2-*t*-butyldimethylsiloxy-3-phenylpropionate was obtained in a 94% yield (*syn*/*anti* = 3/97).

In summary, a novel Mannich-type reaction using *N*-(α-aminoalkyl)benzotriazoles has been developed. Lanthanide triflates are efficient catalysts in the reactions of benzotriazoles with silyl enolates to give the corresponding β-amino ketone or ester derivatives in high yields with high diastereoselectivities.

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References and Notes

1) Kleinman, E. F. "Comprehensive Organic Synthesis," ed by Trost, B. M. Pergamon Press, Oxford (1991), Vol. 2, pp. 893-973. b) Tramontini, M.; Angiolini, L. "Mannich Bases, Chemistry and Uses," CRC Press, Boca Raton 1994, pp. 77-162.
2) (a) Danishefsky, S. J.; Kitahara, T.; McKee, R.; Schuda, P. F. *J. Am. Chem. Soc.* **1976**, *98*, 6717-6718. (b) Wada, M.; Nishihara, Y.; Akiba, K.-y. *Tetrahedron Lett.* **1984**, *25*, 5405-5408. (c) Danishefsky, S. J.; Prisbylla, M.; Lipisko, B. *Tetrahedron Lett.* **1980**, *21*, 805-808.
3) (a) Ojima I.; Inaba, S.; Yoshida, K. *Tetrahedron Lett.* **1977**, 3643-3646. b) Guanti, G.; Narisano, E.; Banfi, L. *Tetrahedron Lett.* **1987**, *28*, 4331-4334. c) Mukaiyama, T.; Kashiwagi, K.; Matsui, S. *Chem. Lett.* **1989**, 1397-1400. d) Mukaiyama, T.; Akamatsu, H. Han, J. S. *Chem Lett.* **1990**, 889-892. e) Onaka, M.; Ohno, R.; Yanagiya, N.; Izumi, Y. *Synlett* **1993**, 141-142. f) Ishihara, K.; Hanaki, N.; Funahashi, M.; Miyata, M.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1721-1730. g) Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* **1995**, 5773-5776.
4) a) Katritzky, A. R.; Rachwal, S; Hitchins, G. J. *Tetrahedron* **1991**, *47*, 2683-2732. b) Katritzky, A. R.; Lan, X. *Chem. Soc. Rev.* **1994**, 363-373. c) Katritzky, A. R.;Yang, Z.; Cundy, D. J. *Aldrichimica Acta* **1994**, 27, 31-38.
5) Katritzky, A. R.; Harris, P. A. *Tetrahedron* **1990**, *46*, 987-996.
6) Katritzky, A. R.; Shobana, N.; Harris, P. A. *Tetrahedron Lett.* **1990**, *31*, 3999-4002.
7) Kobayashi, S. *Synlett* **1994**, 689-701, and references cited therein.
8) (a) Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1995**, 233-234. (b) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195-1202.
9) Quite recently, the SUT group reported lanthanide triflate-catalyzed Mannich-type reaction in aqueous media. Kobayashi, S.; Ishitani, H. *J. Chem. Soc., Chem. Commun.* **1995**, 1379.
10) Lucchini, V.; Prato, M.; Scorrano, G.; Tecilla, P. *J. Org. Chem.* **1988**, *53*, 2251-2258.

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